Remarks

The Office Action mailed March 29, 2005, has been received and carefully reviewed. Reconsideration and withdrawal of the rejections of the claims in view of the claim amendments and accompanying remarks is respectfully requested. New claim 35 is supported by the specification at, for example, page 14, lines 13-26. Claims 1, 6-8, 10, 12-14, 19, 22, 26, 29, 30-34 having been amended, claims 20 and 21 having been canceled, without prejudice, and claim 35 having been added, the pending claim are claims 1-19 and 22-35.

Objection to the Abstract

The abstract of the disclosure is objected to because it is not in single paragraph form. In response, the abstract has been rewritten in accordance with the suggestion of the Examiner. Reconsideration and withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. 112, second paragraph

Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The rejection is respectfully traversed.

Claim 1 is rejected for the recitation of the term "strong reducing agent." Claims 9, 12, 14, 26, 29 and 31-34 are likewise rejected. The Examiner alleges that the term is indefinite since there is no comparative basis for what constitutes "strong". Applicants disagree.

MPEP 2173.05(b) states that when a term of degree is present, the Examiner should determine whether a standard is disclosed or whether one of ordinary skill in the art would be apprised of the scope of the claim. The fact that claim language, including terms of degree, may not be

precise does not *automatically* render the claim indefinite under 35 U.S.C. 112, second paragraph. Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed in light of the specification.

The term "strong reducing agent" is in common use in the chemical arts. Many textbooks and other readily available resources make reference to and give examples of "strong" reducing agents. See, for example, Appendix A of the University of Alberta Laboratory Chemical Safety Manual (Exhibit A), which lists classes of strong reducing agents including metal hydrides and alkyl metals, many of which set forth in the present specification. Further, is well known that strong reducing agents are characterized by large negative reduction potentials, E^0. Reduction potential can be readily determined for any reducing agent of interest from standard sources, for example "Handbook of Chemistry and Physics, 80th Edition, 1999-2000" CRC Press, Washington, D.C. (Tables 1-3 in the Electrochemical Series, pages 8-21 though 8-31) (Exhibit B).

Additionally, the specification itself lists over 20 examples of strong reducing agents (specification at page 14, lines 13-26). This list includes a representative sampling of borohydrides ($E^0 = -0.487$ V), hydrides ($E^0 = -2.23$ V), sodiums ($E^0 = -2.71$) and lithiums ($E^0 = -3.04$). Further, at page 7, last paragraph, the specification describes a representative reducing agent, sodium borohydride, which, when dissolved in aqueous solution, releases a hydrogen atom, a strong reducer. These examples provide ready guidance to the skilled artisan as to the meaning of the term "strong reducing agent".

For at least the foregoing reasons, Applicants submit that ordinary skill in the art *would be apprised* of the scope of the claims that recite a "strong reducing agent."

The Examiner also rejected claim 1, as well as claims 9, 12, 14, 26, 29 and 31-34, for the recitation of "porphyrin-like product," alleging that the claims are indefinite since it is not clear how this product differs from porphyrin itself. Applicants disagree. At the outset, Applicants note that claim 9 does not recite the term "porphyrin-like product." Moreover, with respect to claims 1, 12, 14, 26, 29 and 31-34, the term "porphyrin-like product" is described in a number of places in the specification (see, e.g., page 8 at the second full paragraph). However, in order to advance prosecution of the instant application, claims 1, 12, 14, 26, 29 and 31-34, and claims dependent therefrom are amended to delete recitation of the term "porphyrin-like product." Further, the claims are rewritten to recite monitoring the fluorescence of the treated specimen, sample or tissue, in order to clarify the practice of the method of the invention.

Claims 3, 4, 16 and 17 were rejected as being indefinite because it is allegedly not clear whether the recited percentages are percents by weight or percents by volume. Applicants disagree. The strong reducing agent recited in the claim, sodium borohydride, is a solid. One of skill in the art would readily understand that when an aqueous solution is made by using the solid, the concentration is measured in wt% (w/w) which for aqueous solutions is generally expressed as grams/100mL (w/v) since the density of water is 1 gram/mL. It is respectfully submitted that, in view of the specification and the knowledge common to the art, one of ordinary skill in the art would be apprised of the scope of these claims.

The Examiner recommended that claims 6, 9 and 19 should be amended to recite --and– in place of "or" so as to use proper Markush language. Claims 6 and 9 have been so amended; claim 19 has been amended to delete recitation of the Markush group, rendering the rejection moot with respect to claim 19.

The Examiner points out that the phrase "the fluorescence properties" in claim 13 lacks antecedent basis. Applicants disagree; however claim 13 has been amended to delete the word "properties" as the term is unnecessary.

Claims 14, 19-21, 31 and 34 are alleged to be indefinite in that they do not further limit the physical components of the kit, but merely recite functional methods to be performed with the kit. Applicant disagrees; however claims 14, 19, 31 and 34 have been amended to recite the inclusion of directions (claims 14, 31 and 34) or containers (claim 19) in the kit in order to clarify the invention. Claims 20 and 21 have been canceled, rendering the rejection moot with respect to claims 20 and 21.

Claim 22 is alleged to be indefinite in the recitation of "such as." Applicants disagree; however in order to advance prosecution claim 22 had been amended to delete "such as" as well as the recitation of the types of samples as to avoid any unintentional limitation of the biological sample or specimen.

Claims 32 is rejected as indefinite in that the last step of the method does not relate back to the purpose of the method as stated in the preamble. Applicants disagree; however in order to advance prosecution claim 32 is amended to recite that the extent and spatial distribution of erythrocytes trapped in cerebral tissue microvasculature is indicative of "the likelihood that the subject may develop or has developed the disease."

Reconsideration and withdrawal of the rejection of claims 1-34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention is, accordingly, respectfully requested.

Rejection under 35 U.S.C. 102(b)

Claims 1, 6-8, 12, 14, 20-28, 31 and 34 were rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz (U.S. Pat. No. 4,378,971). This rejection is respectfully traversed.

Applicants note at the outset that claims 21 and 22 have been canceled, rendering the rejection moot as it relates to those claims.

Claim 1 (as amended) of the present invention recites:

> A method for detecting occult blood in a specimen comprising:
> (a) treating the specimen with a reacting solution comprising a strong reducing agent; and
> (b) monitoring the treated specimen for fluorescence, wherein fluorescence indicates the presence of occult blood.

Independent claims 12, 14, 26, 31 and 34 also recite a strong reducing agent. A strong reducing agent is used in the claimed method of detection of occult blood to produce a fluorescent species indicative of the presence of blood in the sample. As described in more detail below, Schwartz does *not* teach a strong reducing agent; instead, it teaches a different type of assay for hemoglobin that is based on *acid* chemistry. The Schwartz assay forms the basis for the well-known HemoQuant® assay, which is described in the present specification as prior art (specification at page 5, first full paragraph, and page 13, first full paragraph). See also Schwartz et al., Clin. Chem. 1983, 29:2061-2067, cited at page 15 of the specification, lines 3-4, and incorporated by reference (see form 1449 and accompanying documents, submitted herewith.)

The present invention, which utilizes a *strong reducing agent* in a *single step* to detect occult blood in a sample, represents a marked improvement over the Schwartz HemoQuant® assay. As stated at page 13 of the present specification, "the strong reducing agent employed [in the present

invention] removes ferric ion more quickly and efficiently than the acid chemistry utilized in the HemoQuant® test, which in turn results in a porphyrin-like product with much greater fluorescence intensity."

The Examiner states that Schwartz teaches a reacting solution that contains a "strong reducing agent or salt." Applicants respectfully submit that this is a misreading of Schwartz. Schwartz teaches a "reducing acid" and a "reducing salt." More particularly, instead of a strong reducing agent, the Schwartz assay utilizes a combination of a "reducing acid," a "reducing salt," and heat to assay hemoglobin. The Examiner further errs in stating that Schwartz teaches that the "strong reducing agent is preferably ferrous oxalate or ferrous sulfate." Ferrous oxalate and ferrous sulfate are not strong reducing agents as their reduction potential, E^0, is a positive + 0.77. Indeed, it is because Schwartz utilizes a very weak reducing agent like ferrous that Schwartz requires the combination of a "reducing acid," a "reducing salt," and heat to produce the fluorescence.

The chemistry used by the present invention to detect occult blood therefore differs significantly from that taught in Schwartz. This is evidenced in a number of different ways. For example, different fluorescence excitation wavelengths are utilized. Treatment of the sample with a strong reducing agent as recited in the pending claims produces a fluorescent species that has strong emission at excitation wavelengths of approximately 480 nm or about 500 nm (e.g., specification at page 8, second full paragraph; claim 8). In contrast, the acid chemistry described Schwartz yields a conversion product that has a different excitation spectrum, more to the blue, and Schwartz teaches excitation wavelengths for use in the assay of 408 nm (Schwartz at col. 5, lines 46-49); 401 nm (Schwartz at col. 8, line 7), and 410 nm (Schwartz at col 8, lines 20). The extreme conditions generated by the combination of "reducing acid," "reducing salt" and heat utilized in Schwartz lead to the formation of a different fluorescent product as evidenced by the different peak wavelength of the fluorescence.

Schwartz also teaches that non-specific (background) fluorescence is problematic and "must be accounted for" via the citric acid blank (Schwartz at col. 7, line 54) in order to produce meaningful information, as acknowledged by the Examiner at page 5 of the Office Action mailed March 29, 2005. In the assay of the present invention, on the other hand, the product of the reduction chemistry has greatly enhanced fluorescence (specification at page 7, fourth full paragraph, last line), and control for background fluorescence is not needed. This greatly enhanced fluorescence results from the use of the strong reducing agent in the claimed method.

Further distinctions that result from, and evidence, the differences in chemistries between the present invention and Schwartz are the times and temperatures required for the chemical reaction. In Schwartz, heat is needed to convert the heme to porphyrin (e.g., col. 6, line 34), and the reaction is preferably conducted at about 120°C for 90 minutes, although the reaction will proceed (quite slowly) with temperatures in the range of 60°C to 100°C (Schwartz at col. 6, lines 11-14). In the present invention, the use of the strong reducing agent allows the reaction to proceed at room temperature (e.g., specification at page 13, first full paragraph) and in under 60 minutes, if not substantially faster (e.g., specification at page 14, first full paragraph).

Finally, Schwartz provides no reason to believe that ferrous sulfate or ferrous oxalate, as "reducing salts," would be effective to produce fluorescence in the sample without the further addition of the "reducing acid" (oxalic acid) to produce the required strong *acidic* environment (Schwartz at col., 6, lines 33-34), and heat, as described above. This further evidences that the chemistry employed in the present invention is very different from that described in Schwartz.

In sum, because it does not, for example, teach a strong reducing agent, Schwartz does not teach each and every element of pending claims 1, 6-8, 12, 14, 20, 23-28, 31 and 34. Reconsideration and withdrawal of the rejection of claims 1, 6-8, 12, 14, 20, 23-28, 31 and 34 under 35 U.S.C. 102(b) as being anticipated by Schwartz is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 5, 9-11, 13 and 33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz (U.S. Pat. No. 4,378,971). This rejection is respectfully traversed.

As stated above, Applicants maintain that the chemistry used in the present invention differs significantly from that described in Schwartz. In particular, Schwartz does not teach treatment of a sample or specimen with a strong reducing agent. Nor is the use of a strong reducing agent obvious in view of Schwartz, as Schwartz teaches an acid chemistry and does provide any motivation for using a strong reducing agent in the chemical conversion of porphyrin. Further evidencing these different chemistries, the excitation wavelength used to detect sample fluorescence in the present invention is different (e.g., 408 nm compared to Schwartz at 480 nm) and it is not necessary to heat the reaction or control for background fluorescence in the present invention as it is in the method taught in Schwartz.

For at least these reasons, Applicants assert that the teachings of Schwartz do not render claims 5, 9-11, 13 and 33 obvious. Reconsideration and withdrawal of the rejection of claims 9-11, 13 and 33 under 35 U.S.C. 103(a) as being unpatentable over Schwartz is therefore respectfully requested.

Claims 2-4 and 15-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz (U.S. Pat. No. 4,378,971), in view of Kerwin et al. (U.S. Pat. No. 5,929,031). This rejection is respectfully traversed.

As stated above, Applicants maintain that Schwartz does not teach or suggest treatment of a sample or specimen with a strong reducing agent to detect occult blood in a sample or specimen. In particular, Schwartz does not teach sodium borohydride.

This deficiency is not corrected by Kerwin et al., which teaches the use of sodium borohydride in solution with hemoglobin for the purpose of stabilizing the hemoglobin. The hemoglobin taught in Kerwin et al. is not iron-free, and there is no teaching or suggestion that sodium borohydride is added to the hemoglobin solution to demetalate the heme or to cause fluorescence. Instead what is taught by Kerwin et al. is a deoxygenated solution of hemoglobin that can be maintained by the addition of a low level of a reducing agent, such as sodium borohydride. Indeed, one of the disadvantages of the prior art noted by Kerwin et al. is that the addition of ascorbate at relatively high concentrations to stabilize deoxygenated hemoglobin solutions resulted in a significant release of free iron (Kerwin et al. at col. 4, lines 49-51). Thus, by teaching the use of sodium borohydride to *stabilize* the heme, Kerwin et al. teaches away from the present invention which utilizes sodium borohydride to produce a fluorescent species indicative of occult blood in the sample.

For at least these reasons, Applicants assert that the teachings of Schwartz, alone or in combination with the teachings of Kerwin et al., do not render claims 2-4 and 15-19 obvious. Reconsideration and withdrawal of the rejection of claims 2-4 and 15-19 under 35 U.S.C. 103(a) as being unpatentable over Schwartz in view of Kerwin et al. is therefore respectfully requested.

Claims free of the prior art

Applicants acknowledge the Examiner's statement that claims 29, 30 and 32 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and, in the case of claim 30, to include all of the limitations of the base claim and any intervening claims. It is respectfully submitted that, for reasons described above, the Examiner's rejection(s) of claims 29, 30 and 32 have been overcome.

Summary

It is respectfully submitted that the pending claims 1-19, 22-35 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Liu et al.

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

Sept 29, 2005
Date

By: Victoria A. Sandberg
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612) 305-1226

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 201893415US Date of Deposit: Sept. 29, 2005
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Deb Schurmann
Name: Deb Schurmann